

What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, said nucleic acid molecule encoding at least a portion of ion-x.
2. The isolated nucleic acid molecule of claim 1 comprising a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.
3. The isolated nucleic acid molecule of claim 1 comprising a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51 and SEQ ID NOS:107 and 108.
4. The isolated nucleic acid molecule of claim 1 comprising a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51 and SEQ ID NOS:107 and 108.
5. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is DNA.
6. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is RNA.
7. An expression vector comprising a nucleic acid molecule of any one of claims 1 to 4.
8. The expression vector of claim 7 wherein said nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51 and SEQ ID NOS:107 and 108.
9. The expression vector of claim 7 wherein said vector is a plasmid.

10. The expression vector of claim 7 wherein said vector is a viral particle.

11. The expression vector of claim 10 wherein said vector is selected from the group consisting of adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses.

12. The expression vector of claim 7 wherein said nucleic acid molecule is operably connected to a promoter selected from the group consisting of simian virus 40, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metallothionein.

13. A host cell transformed with an expression vector of claim 8.

14. The transformed host cell of claim 13 wherein said cell is a bacterial cell.

15. The transformed host cell of claim 14 wherein said bacterial cell is E. coli.

16. The transformed host cell of claim 13 wherein said cell is yeast.

17. The transformed host cell of claim 16 wherein said yeast is S. cerevisiae.

18. The transformed host cell of claim 13 wherein said cell is an insect cell.

19. The transformed host cell of claim 18 wherein said insect cell is S. frugiperda.

20. The transformed host cell of claim 13 wherein said cell is a mammalian cell.

21. The transformed host cell of claim 20 wherein mammalian cell is selected from the group consisting of chinese hamster ovary cells, HeLa cells, African green monkey kidney cells, human HEK-293 cells, and murine 3T3 fibroblasts.

22. An isolated nucleic acid molecule comprising at least 10 nucleotides, said nucleic acid molecule comprising a nucleotide sequence complementary to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108.

23. The nucleic acid molecule of claim 22 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108.

24. The nucleic acid molecule of claim 23 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108.

25. A composition comprising a nucleic acid molecule of any one of claims 1 to 4 or 22 and an acceptable carrier or diluent.

26. A composition comprising a recombinant expression vector of claim 7 and an acceptable carrier or diluent.

27. A method of producing a polypeptide that comprises a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, said method comprising the steps of:

- a) introducing a recombinant expression vector of claim 7 into a compatible host cell;
- b) growing said host cell under conditions for expression of said polypeptide; and
- c) recovering said polypeptide.

28. The method of claim 27 wherein said host cell is lysed and said polypeptide is recovered from the lysate of said host cell.

29. The method of claim 27 wherein said polypeptide is recovered by purifying the culture medium without lysing said host cell.

30. An isolated polypeptide encoded by a nucleic acid molecule of claim 1.

31. The polypeptide of claim 30 wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

32. The polypeptide of claim 30 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

33. The polypeptide of claim 30 wherein said sequence homologous to a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, comprises at least one conservative amino acid substitution compared to the sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

34. The polypeptide of claim 30 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

35. A composition comprising a polypeptide of claim 30 and an acceptable carrier or diluent.

36. An isolated antibody which binds to an epitope on a polypeptide of claim 30.

37. The antibody of claim 36 wherein said antibody is a monoclonal antibody.

38. A composition comprising an antibody of claim 36 and an acceptable carrier or diluent.

39. A method of inducing an immune response in a mammal against a polypeptide of claim 30 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.

40. A method for identifying a compound which binds ion-x comprising the steps of:

- contacting ion-x with a compound; and
- determining whether said compound binds ion-x.

41. The method of claim 40 wherein the ion-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

42. The method of claim 40 wherein binding of said compound to ion-x is determined by a protein binding assay.

43. The method of claim 40 wherein said protein binding assay is selected from the group consisting of a gel-shift assay, Western blot, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, and ELISA.

44. A compound identified by the method of claim 40.

45. A method for identifying a compound which binds a nucleic acid molecule encoding ion-x comprising the steps of:

- contacting said nucleic acid molecule encoding ion-x with a compound; and
- determining whether said compound binds said nucleic acid molecule.

46. The method of claim 45 wherein binding is determined by a gel-shift assay.

47. A compound identified by the method of claim 45.

48. A method for identifying a compound which modulates the activity of ion-x comprising the steps of:

- a) contacting ion-x with a compound; and
- b) determining whether ion-x activity has been modulated.

49. The method of claim 48 wherein the ion-x comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110.

50. The method of claim 48 wherein said activity is neuropeptide binding.

51. The method of claim 48 wherein said activity is neuropeptide signaling.

52. A compound identified by the method of claim 48.

53. A method of identifying an animal homolog of ion-x comprising the steps:

- a) comparing the nucleic acid sequences of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108; and
- b) identifying nucleic acid sequences of the animal that are homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108.

54. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108, is performed by DNA hybridization.

55. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:51, and SEQ ID NOS:107 and 108, is performed by computer homology search.

56. A method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one ion channel that is expressed in the brain, wherein the ion channel comprises an amino acid sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, and allelic variants thereof, and wherein the nucleic acid corresponds to a gene encoding the ion channel; and

(b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of the ion channel correlates with an increased risk of developing the disorder.

57. A method according to claim 56, wherein the assaying step comprises at least one procedure selected from the group consisting of:

a) comparing nucleotide sequences from the human subject and reference sequences and determining a difference of at least a nucleotide of at least one codon between the nucleotide sequences from the human subject that encodes an ion-x allele and an ion-x reference sequence;

(b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences;

(c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and

(d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

58. A method of screening for an ion-x mental disorder genotype in a human patient, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from said patient, said nucleic acid including sequences corresponding to alleles of ion-x; and
(b) detecting the presence of one or more mutations in the ion-x alleles;

wherein the presence of a mutation in an ion-x allele is indicative of a mental disorder genotype.

59. The method according to claim 58 wherein said biological sample is a cell sample.

60. The method according to claim 58 wherein said nucleic acid is DNA.

61. The method according to claim 58 wherein said nucleic acid is RNA.

62. A kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association:

(a) an oligonucleotide useful as a probe for identifying polymorphisms in a human ion-x gene, the oligonucleotide comprising 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human ion-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and

(b) a media packaged with the oligonucleotide, said media containing information for identifying polymorphisms that correlate with a mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

63. A method of identifying an ion channel allelic variant that correlates with a mental disorder, comprising steps of:

(a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny;

(b) detecting in the nucleic acid the presence of one or more mutations in an ion channel that is expressed in the brain, wherein the ion channel

comprises an amino acid sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, and allelic variants thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the ion channel;

wherein the one or more mutations detected indicates an allelic variant that correlates with a mental disorder.

64. A purified and isolated polynucleotide comprising a nucleotide sequence encoding ion-x allelic variant identified according to claim 63.

65. A host cell transformed or transfected with a polynucleotide according to claim 64 or with a vector comprising the polynucleotide.

66. A purified polynucleotide comprising a nucleotide sequence encoding ion-x of a human with a mental disorder;

wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110 under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and
(b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and

wherein the polynucleotide that encodes ion-x amino acid sequence of the human differs from the sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110 by at least one residue.

67. A vector comprising a polynucleotide according to claim 66.

68. A host cell that has been transformed or transfected with a polynucleotide according to claim 66 and that expresses the ion-x protein encoded by the polynucleotide.

69. A method for identifying a modulator of biological activity of ion-x comprising the steps of:

(a) contacting a cell according to claim 68 in the presence and in the absence of a putative modulator compound;

(b) measuring ion-x biological activity in the cell;

wherein decreased or increased ion-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

70. A method to identify compounds useful for the treatment of a disorder, said method comprising the steps of:

(a) contacting a composition comprising ion-x with a compound suspected of binding ion-x;

(b) detecting binding between ion-x and the compound suspected of binding ion-x;

wherein compounds identified as binding ion-x are candidate compounds useful for the treatment of a disorder.

71. A method for identifying a compound useful as a modulator of binding between ion-x and a binding partner of ion-x comprising the steps of:

(a) contacting the binding partner and a composition comprising ion-x in the presence and in the absence of a putative modulator compound;

(b) detecting binding between the binding partner and ion-x;

wherein decreased or increased binding between the binding partner and ion-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a disorder.

72. A method according to claim 70 or 71 wherein the composition comprises a cell expressing ion-x on its surface.

73. A method according to claim 72 wherein the composition comprises a cell transformed or transfected with a polynucleotide that encodes ion-x.

74. A chimeric receptor comprising at least 5 amino acid residues, said receptor comprising at least a portion of a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102, and SEQ ID NOS:109 and 110.

75. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:52 to SEQ ID NO:102 and SEQ ID NOS:109 and 110, said nucleic acid molecule encoding at least a portion of ion-x.

76. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NO:106.

77. An isolated nucleic acid molecule comprising a nucleotide sequence homologous to a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

78. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

79. The isolated nucleic acid molecule of claim 76 wherein said nucleic acid molecule is DNA.

80. The isolated nucleic acid molecule of claim 76 wherein said nucleic acid molecule is RNA.

81. An expression vector comprising a nucleic acid molecule of any one of claims 76 to 78.

82. The expression vector of claim 81 wherein said nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

83. A host cell transformed with an expression vector of claim 81.

84. An isolated nucleic acid molecule comprising at least 10 nucleotides, said nucleic acid molecule comprising a nucleotide sequence complementary to a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

85. The nucleic acid molecule of claim 84 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

86. The nucleic acid molecule of claim 85 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104.

87. A composition comprising a recombinant expression vector of claim 81 and an acceptable carrier or diluent. ✓

88. A method of producing a polypeptide that comprises a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106, said method comprising the steps of:

- introducing a recombinant expression vector of claim 81 into a compatible host cell;
- growing said host cell under conditions for expression of said polypeptide; and
- recovering said polypeptide.

89. An isolated polypeptide encoded by a nucleic acid molecule of claim 76.

90. The polypeptide of claim 89 wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106.

91. The polypeptide of claim 89 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106.

92. The polypeptide of claim 89 wherein said sequence homologous to a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106, comprises at least one conservative amino acid substitution compared to the sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106.

93. The polypeptide of claim 89 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106.

94. A composition comprising a polypeptide of claim 89 and an acceptable carrier or diluent.

95. An isolated antibody which binds to an epitope on a polypeptide of claim 83.

96. The antibody of claim 95 wherein said antibody is a monoclonal antibody.

97. A method of inducing an immune response in a mammal against a polypeptide of claim 89 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.

98. A method for identifying a compound which binds an ion channel encoded by a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 comprising the steps of:

- a) contacting said ion channel with a compound; and
- c) determining whether said compound binds said ion channel.

99. The method of claim 98 wherein the ion channel comprises an amino acid sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NO:106.

100. A compound identified by the method of claim 98.

101. A method for identifying a compound which binds a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 comprising the steps of:

- a) contacting said nucleic acid molecule with a compound; and
- b) determining whether said compound binds said nucleic acid

molecule.

102. A compound identified by the method of claim 101.

103. A method for identifying a compound which modulates the activity of an ion channel encoded by a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 comprising the steps of:

- a) contacting said ion channel with a compound; and
- b) determining whether ion channel activity has been modulated.

104. The method of claim 103 wherein the ion channel comprises an amino acid sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NO:106.

105. A compound identified by the method of claim 103.

106. A method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one ion channel that is expressed in the brain, wherein the ion channel comprises an amino acid sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NO:106, and allelic variants thereof, and wherein the nucleic acid corresponds to a gene encoding the ion channel; and

(b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of the ion channel correlates with an increased risk of developing the disorder.

107. A kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association:

(a) an oligonucleotide useful as a probe for identifying polymorphisms in a human ion channel gene, the oligonucleotide comprising 6-50 nucleotides in a sequence that is identical or complementary to a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and

(b) a media packaged with the oligonucleotide, said media containing information for identifying polymorphisms that correlate with a mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

108. A method of identifying an ion channel allelic variant that correlates with a mental disorder, comprising steps of:

(a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny;

(b) detecting in the nucleic acid the presence of one or more mutations in an ion channel that is expressed in the brain, wherein the ion channel comprises an amino acid sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NO:106, and allelic variants thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the ion channel;

wherein the one or more mutations detected indicates an allelic variant that correlates with a mental disorder.

109. A purified and isolated polynucleotide comprising a nucleotide sequence encoding ion-x allelic variant identified according to claim 108.

110. A host cell transformed or transfected with a polynucleotide according to claim 109 or with a vector comprising the polynucleotide.

111. A method for identifying a modulator of biological activity of an ion channel encoded by a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 comprising the steps of:

(a) contacting a cell according to claim 110 in the presence and in the absence of a putative modulator compound;

(b) measuring ion channel biological activity in the cell;
wherein decreased or increased ion channel biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

112. A method to identify compounds useful for the treatment of a disorder, said method comprising the steps of:

(a) contacting a composition comprising an ion channel encoded by a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 with a compound suspected of binding said ion channel;

(b) detecting binding between said ion channel and the compound suspected of binding said ion channel;

wherein compounds identified as binding said ion channel are candidate compounds useful for the treatment of a disorder.

113. A method for identifying a compound useful as a modulator of binding between an ion channel encoded by a sequence selected from the group consisting of SEQ ID NO:103 and SEQ ID NO:104 and a binding partner of said ion channel comprising the steps of:

(a) contacting the binding partner and a composition comprising said ion channel in the presence and in the absence of a putative modulator compound;

(b) detecting binding between the binding partner and said ion channel;

wherein decreased or increased binding between the binding partner and said ion channel in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a disorder.

114. A method according to claim 112 or 113 wherein the composition comprises a cell expressing said ion channel on its surface.

115. A method according to claim 114 wherein the composition comprises a cell transformed or transfected with a polynucleotide that encodes said ion channel.

116. A chimeric receptor comprising at least 5 amino acid residues, said receptor comprising at least a portion of a sequence selected from the group consisting of SEQ ID NO:105 and SEQ ID NOS:106.